510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k121842

B. Purpose for Submission:

New device

C. Measurand:

Glycosylated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative, chemiluminescent microparticle immunoassay (CMIA)

E. Applicant:

Axis-Shield Diagnostics Limited

F. Proprietary and Established Names:

ARCHITECT HbA1c Reagent

ARCHITECT HbA1c Calibrators (A-F)

G. Regulatory Information:

Regulation Description	Product Code	Device Class	Regulation	Panel
Glycosylated Hemoglobin Assay	LCP	II	21 CFR § 864.7470	Hematology, 81
Calibrator	JIT	II	21 CFR § 862.1150	Chemistry, 75

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   The ARCHITECT HbA1c assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of percent hemoglobin A1c (HbA1c) in human

whole blood on the ARCHITECT *i* System. Percent HbA1c measurements are used for monitoring long term glycemic control in diabetic patients.
The ARCHITECT HbA1c Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of percent hemoglobin A1c (HbA1c) in human whole blood.

3. Special conditions for use statement(s):

- For prescription use only
- Should not be used for the diagnosis of diabetes mellitus
- Should not be used in monitoring daily glucose control
- Should not be used to replace daily home testing of urine and blood glucose levels
- Should not be used for analyzing samples from patients with conditions causing shortened red blood cell survival, such as hemolytic diseases, pregnancy, and significant acute or chronic blood loss.
- Should not be used for analyzing samples from patients with total hemoglobin levels of less than 7 or greater than 21 g/dL.
- Hemoglobinopathies may interfere with glycated hemoglobin analysis. Samples containing the following hemoglobin variants have been shown to interfere with the assay: Hemoglobin D, Hemoglobin E, Hemoglobin F (>9%), and Hemoglobin S.

4. Special instrument requirements:

For use on the ARCHITECT i 2000SR System

I. Device Description:

The ARCHITECT HbA1c reagent kit consists of 3 reagents:

- Microparticles: Silica surface microparticles in acetate buffer with zinc chloride and surfactants.
- Conjugate: Anti-HbA1c (mouse, monoclonal) acridinium-labeled conjugate in MES buffer with surfactants.
- Pre-treatment: Pre-treatment reagent (lysis buffer) containing detergent with sodium azide preservative.

The ARCHITECT HbA1c Calibrator kit consists of 6 levels of calibrators (A-F) containing approximately 4.0%, 5.5%, 7.5%, 9.0%, 12% and 14.5% HbA1c. Calibrators A through F are *in vitro*-glycated human whole blood.
All human source materials were tested by FDA approved methods and found to be negative for the presence of HBs Ag and antibody to HIV1/HIV2, and HCV.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   AxSYM HbA1c Reagent Set and Calibrator set

2. Predicate 510(k) number(s):

   k072686

3. Comparison with predicate:

Similarities and Differences: Reagent		
Item	Candidate Device ARCHITECT HbA1c (k121842)	Predicate Device AxSym HbA1c (k072686)
Intended Use/ Indications for Use	The ARCHITECT HbA1c assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of percent hemoglobin A1C (HbA1c) in human whole blood on the ARCHITECT i System. Percent HbA1c measurements are used for monitoring long term glycemic control in diabetic patients.	AxSym HbA1c is an immunoassay for the quantitative determination of percent hemoglobin A1c (HbA1c) in whole blood samples on the AxSYM System. Percent HbA1c measurements are used in the clinical management of diabetes to assess the long-term efficacy of diabetic control.
Specimen Type	Whole Blood : Dipotassium EDTA, Fluoride Oxalate, Sodium Fluoride/Potassium EDTA, Sodium Fluoride/Sodium EDTA	Whole Blood: Fluoride Oxalate, Sodium Fluoride/Potassium Oxalate, Sodium Fluoride/Sodium EDTA, Potassium EDTA
Assay Principle	Chemiluminescent Microparticle Immunoassay	Microparticle Enzyme Immunoassay
Substrate	Acridinium Tracer	4-Methylumbellifery Phosphate
Measuring Range	4.0-14.5% HbA1c	Same

<table>
<tr>
<td>Expected Values</td>
<td>ADA 2012 Standards of Medical Care Recommendations:
<table>
<tr><td>HbA1c (%)</td><td>Glycemic Goal</td></tr>
<tr><td><8</td><td>Less Stringent</td></tr>
<tr><td><7</td><td>General Goal</td></tr>
<tr><td><6.5</td><td>More Stringent</td></tr>
<tr><td><5.7</td><td>Non-Diabetic Goal</td></tr>
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</td>
<td>Central 95% of the population was 4.6-6.0% HbA1c (reference range study)</td>
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Similarities and Differences: Calibrator		
Item	**Candidate Device ARCHITECT HbA1c Calibrators (k121842)**	**Predicate Device AxSYM HbA1c Calibrators (k072686)**
Intended Use/ Indications for Use	Calibrators are for the calibration of the ARCHITECT i System when used for the quantitative determination of percent hemoglobin A1c (HbA1c) in human whole blood.	Calibrators are for the calibration of the AxSYM System when used for the quantitative determination of percent hemoglobin A1c (HbA1c) in whole blood samples.
Format	Frozen	Same
Levels	Six levels (4.0%, 5.5%, 7.5%, 9.0%,12.0% and 14.5%) HbA1c	Same
Storage Conditions	Shipped frozen and must be stored at -20˚C or colder in an upright position. Return calibrators to carton and store at -20˚C or colder immediately after use.	Standard Calibrator Pack must be stored at -20˚C until first used and then at 2-8 ˚C for a maximum of 30 days.

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition

CLSI EP6-A : Evaluation of the Linearity of Quantitative Measuring Procedures: A Statistical Approach; Approved Guideline

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

CLSI EP7-A : Interference Testing in Clinical Chemistry, Approved Guideline

EN 13460 06: Stability Testing of In Vitro Diagnostic Reagents

L. Test Principle:

The ARCHITECT HbA1c assay is a two-step pre-treatment immunoassay for the quantitative determination of percent hemoglobin A1c (% HbA1c) in human whole blood using CMIA technology, with flexible assay protocols, referred to as Chemiflex.

Sample is incubated with pre-treatment reagent to lyse the red blood cells. Pre-treated sample is then incubated with magnetic microparticles with a silica surface. Hemoglobin and HbA1c in the sample bind to the silica surface of the microparticles. Following a wash cycle, anti-HbA1c acridinium- labeled conjugate chemiluminescent reaction is measured as relative light units (RLUs).

The hemoglobin and HbA1c that are bound to the surface of the microparticles represents the total percentage present in the sample however, only the HbA1c result is required to determine the % HbA1c in the sample. A direct relationship exists between the amount of HbA1c in the sample and the RLUs detected by the ARCHITECT i System optics.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision studies were performed in accordance with the CLSI EP5-A2 guideline. Two ARCHITECT i 2000SR analyzers and two lots of ARCHITECT HbA1c reagents and calibrators were used throughout the study. One reagent lot and one calibrator lot were assigned to each instrument.

Three levels of HbA1c, derived from natural patient samples were assayed for imprecision assessments in replicates of two, twice daily, for 20 days (n=80) observations for each control per combination. A summary of the imprecision data is summarized in the tables below:

			Within-Run Precision		Between-Run Precision		Between-Day Precision		Total Precision	
n	Sample	Mean (% HbA1c)	SD	%CV	SD	%CV	SD	%CV	SD	%CV
80	1	5.1	0.14	2.8	0.11	2.3	0.00	0.0	0.18	3.6
	2	9.9	0.28	2.8	0.23	2.3	0.10	1.0	0.38	3.8
	3	6.2	0.14	2.3	0.10	1.6	0.08	1.3	0.19	3.1
80	1	5.1	0.09	1.8	0.05	1.1	0.10	1.9	0.15	2.9
	2	9.8	0.21	2.1	0.16	1.7	0.08	0.8	0.27	2.8
	3	6.3	0.15	2.4	0.08	1.3	0.08	1.3	0.19	3.0

b. Linearity/assay reportable range:

Linearity was evaluated according to CLSI-06A. A high HbA1c patient sample (15.8% HbA1c) was diluted in Calibrator A (4.0% HbA1c) to achieve a total of 9 intermediate samples covering the assay range. All intermediate dilutions were run in replicates of 5 with randomized run orders. The mean observed %HbA1c value was determined for each intermediate dilution and plotted versus the relative analyte concentration.

The linear regression equation is as follows:

$y=0.96x- 0.09, r^2 = 0.98$

The study supports that the Architect HbA1c assay is linear across the range of 4.0 to 15.8 % HbA1c.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability:

The Architect HbA1c assay standardization is traceable to the International Federation of Clinical Chemistry (IFCC) reference calibrators. The Architect HbA1c assay is NGSP certified. The NGSP certification expires in one year. See NGSP website for current certification at http://www.ngsp.org.

Two different units of measure are provided to the users: NGSP equivalent units (%HbA1c) and IFCC equivalent units (mmol/mol).

Value Assignment

The ARCHITECT HbA1c calibrators are aligned to IFCC reference calibrators through internal value assignment in which calibrator values must meet the sponsor's pre-determined acceptance criteria fall within a set specification, determined by the manufacturer.

The sponsor recommends using commercially available control material containing HbA1c.

Stability

Shelf-life claims: Un-opened calibrators can be stored at -20°C until expiration date (52 weeks).

Open-vial claims: The recommended storage condition for in-use calibrators is -20°C and is stable for 30 days. The labeling recommends not to freeze-thaw calibrator more than 3 times.

On-board stability for the ARCHITECT HbA1c was established by real time studies on the ARCHITECT i2000SR instrument and demonstrated on-board reagent stability of 30 days. The ARCHITECT HbA1c is stable until the expiration date printed on the label when stored at 2 to 8°C.

The storage and stability study protocols and acceptance criteria provided by the sponsor were reviewed and found acceptable to support the claimed conditions.

d. Detection limit:

The Limit of Blank (LoB) was determined by assaying an *in vitro* non glycated hemoglobin material (blank) for a total of 60 measurements. Each sample was assayed in two runs over 2 days using two ARCHITECT i2000SR analyzers with two reagent lots (each lot tested on each analyzer) to give a total of four data sets with 15 results per sample according to CLSI guideline EP17A.

The Limit of Detection (LoD) was determined by assaying 4 low level (< 4.0%) HbA1c samples in two runs over two days using two ARCHITECT i2000SR analyzers with two reagent lots (each lot tested on each analyzer) to give a total of 60 results per reagent/instrument combination (15 results per sample) according to CLSI guideline EP17A.

Limit of Quantitation: The sponsor states that the standard calibrators for the assay have a lower limit of 4.0% and the instrument will report results below 4% as "<4.0%".

The ARCHTECT HbA1c assay detection limits are summarized in the table below:

ARCHITECT i2000SR HbA1c

LoB	**LoD**	**LoQ**
2.7%	2.8%	4.0%

The assay has a reportable range on the ARCHITECT HbA1c of 4.0-15.8%.

e. Analytical specificity:

i.) An interference study was performed based on CLSI EP7-A2 guideline to assess common or known substances that could interfere with the ARCHITECT HbA1c assay. The potential interferents listed below were spiked into human EDTA whole blood samples with different levels of % HbA1c (approximately 6.5 and > 8.0% HbA1c). Each sample was tested in duplicate. The % HbA1c values of the spiked samples were compared to reference samples. The sponsor considered ≤ ±10% as their acceptance criterion.

The interferents study results are summarized in the following table

Potential Interferent	Concentration at which no significant interference (≥±10%) was observed
Bilirubin	50 mg/dL
Total Protein	5 g/dL*
Triglycerides	1600 mg/dL
Rheumatoid Factor	800 IU/mL

Acetylsalicylate	66 mg/dL
Ascorbic Acid	50 mg/dL
Sodium Cyanate (Carbamylated Hb)	50 mg/dL
Urea	667 mg/dL

* 5g/dL of total protein were added to a whole blood sample with a total protein concentration of approximately 7g/dL

ii.) Effect of Total Hemoglobin Levels on Percent HbA1c:
A hemoglobin concentration interference study was performed with the ARCHITECT HbA1c assay by testing three IFCC reference controls with a target value of 6.96% HbA1c. Three levels of HbA1c control samples were used in this study with hemoglobin concentrations of 7g/dL, 13g/dL and 20g/dL. These samples were analyzed in duplicate using the ARCHITECT HbA1c assay. The mean concentration and %CV for the samples of each hemoglobin concentration sample were calculated. The difference and percent difference between the low hemoglobin and the high hemoglobin and normal hemoglobin concentration sample were calculated. The percent difference of HbA1c was all within the sponsor acceptance criteria of ±10%. The sponsor concluded that total hemoglobin values between the ranges of 7 to 20 g/dL do not interfere with the ARCHITECT HbA1c assay.

iii.) Effect of labile glycated A1c with the ARCHITECT HbA1c assay. High concentrations of glucose (1400 mg/dL) were spiked into 2 human EDTA whole blood samples with different levels of % HbA1c (approximately 6.5and > 8.0%) and incubated for 3 hours at 37°C to generate labile glycated hemoglobin. Mean percent differences were obtained when comparing samples with glucose levels of 1400 mg/dL to the reference samples (control samples containing no labile HbA1c). The sponsor concluded that labile A1c does not interfere with the ARCHITECT HbA1c assay.

iv.) A hemoglobin variant interference study was performed using samples known to contain Hemoglobin variants HBA2, HbC, HbD, HbE, HbF HbJ and HbS. These variant samples were tested in duplicate using the ARCHITECT HbA1c assay on ARCHITECT i 2000SR analyzer. All variants tested showed <10% bias at a HbA1c concentrations between 4.7 -11.3%.
The sponsor states in the labeling that hemoglobinopathies may interfere with glycated hemoglobin analysis and that samples containing the following hemoglobin variants have been shown to interfere with the ARCHITECT HbA1c assay: Hemoglobin D, Hemoglobin E, Hemoglobin F (>9%) and Hemoglobin S.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study using human EDTA whole blood specimens (n=127) was performed based on NCCLS Document CLSI EP9-A2 guideline. Each sample was analyzed in singlicate on the candidate and predicate device. The sample range tested was 4.07 to 13.61% HbA1c. The linear regression correlation is summarized below:

Method Comparison

Concentration Range (% HbA1c)	Correlation Coefficient (r) (95% CI)	Slope (95% CI)	Intercept (95% CI)
Architect 4.07-13.61	0.95 (0.93,0.96)	1.04 (0.97,1.12)	-0.07 (-0.67, 0.37)

b. Matrix comparison:

A matrix study was performed to determine the suitability of different anticoagulant collection tube types for use in the ARCHITECT HbA1c assay. Twenty (20) matched non-diabetic samples and twenty (20) matched diabetic samples were obtained for a total of 40 samples in the following blood collection tubes: Dipotassium-EDTA (control), Sodium-Fluoride/potassium-EDTA, Fluoride oxalate, and Lithium Heparin. The actual observed HbA1c levels of samples ranged from 4.4% to 13.3% HbA1c to include samples across the measurable range of the assay. The results are as follows:

K-EDTA Control vs Tube Types			
Tube type	**Linear fit**		
	Slope (95% CI)	**Intercept (95% CI)**	**r value**
Sodium Fluoride/Sodium EDTA	1.06	-0.40	0.99
	1.03 to 1.09	-0.62 to -0.19	
Fluoride Oxalate	1.07	-0.02	0.99
	1.04 to 1.11	-0.26 to 0.23	

Sodium Fluoride/Potassium EDTA	1.03	-0.10	0.99
	1.00 to 1.06	-0.34 to 0.14	

When measured against the Dipotassium-EDTA control tube type, sodium-fluoride/potassium-EDTA, sodium-fluoride/sodium-EDTA and fluoride oxalate blood collection tubes have been shown to be acceptable for the ARCHITECT HbA1c assay with a percent difference of less than 10%.

Lithium heparin blood collection tubes have been shown to be unacceptable for the ARCHITECT HbA1c assay.

The labeling states do not use lithium heparin tubes with this assay.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

*b. Clinical specificity**:***

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:

Hemoglobin A1c expected value range was cited from American Diabetes Association Standards of Medical Care in Diabetes 2012, 35 (Supplement 1), S11-S63

HbA1c Value	Glycemic Goal
< 8% HbA1c (64 mmol/mol)	Less stringent
< 7% HbA1c (53 mmol/mol)	General (Non-Pregnant Adults)
< 6.5% HbA1c (48 mol/mol)	More stringent

As recommended by the ADA, patients in the range of 5.7 - 6.4% HbA1c (39-46 mmol/mol) would be in the category of increased risk for diabetes.

N. Proposed Labeling

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.